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PRINCIPAL INVESTIGATOR: Jennifer L. Kelsey, Ph.D.

CONTRACTING ORGANIZATION: Stanford University
Stanford, CA 94305-5401

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14. ABSTRACT
This was a two-year randomized trial of the effects of oral contraceptives on bone mass and stress fracture incidence among 150 female competitive distance runners of ages 18-26 years. The Coordinating Center is at Stanford University and bone mass was measured at five sites: Massachusetts General Hospital, University of California Los Angeles, University of Michigan, Stanford University/Palo Alto VA Medical Center, and Helen Hayes Hospital in West Haverstraw NY. Two manuscripts have been completed and are about to be submitted for publication. One manuscript, "Randomized trial of the effect of oral contraceptives on bone mass and stress fractures in female runners," concludes that oral contraceptives may reduce the risk for stress fracture, but our data are inconclusive. Oligo/amenorrheic athletes with low bone mass should be advised to gain weight, increase dietary calcium, and take steps to resume normal menses; they may benefit from oral contraceptives, but again the evidence is not conclusive. The second manuscript, "Risk factors for stress fracture among young female cross-country runners," found that a history of stress fractures, lower bone mass, lower dietary calcium intake, younger chronological age, younger age at menarche, and possibly a history of irregular menstrual periods were associated with an increased risk.

15. SUBJECT TERMS
bone mass, oral contraceptives, physical activity, randomized trial, epidemiology, stress fracture, osteoporosis

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(5) INTRODUCTION

Highly trained female athletes may experience loss of menses because of their participation in intense physical activity. Previous cross-sectional research has shown that women with exercise-induced menstrual irregularities have a significantly higher frequency of stress fractures and low bone mass than normally menstruating controls. Longitudinal studies suggest that these women are losing bone mass over time. Low serum estrogen levels are believed to be a principal cause of the bone loss. If so, re-establishing normal estrogen levels in these women should prevent or retard bone loss and decrease the incidence of stress fracture. This study was a two-year randomized trial of the effect of oral contraceptives on bone mass and stress fracture incidence among 150 female cross country runners in the age range 18-25 years. The Coordinating Center is at Stanford University and bone mass was measured at five sites: the Massachusetts General Hospital, the University of California Los Angeles, the University of Michigan, Stanford University/Palo Alto VA Medical Center, and the Helen Hayes Hospital in West Haverstraw, NY. Athletes were recruited mostly from the areas around these five clinical sites.

(6) BODY

Below we (a) summarize our progress through year 8, (b) provide abstracts from two manuscripts about to be submitted for publication, and (c) present our plans for additional statistical analyses.

(a) Progress through year 8:

One hundred fifty eligible female runners were randomized, of whom 124 (83%) attended at least one follow-up appointment and 96 (64%) attended both, and at average of 14.4 and 26.6 months, respectively. Three additional women provided information on stress fracture occurrence for an average of 7.9 months after baseline. Data collection has been completed, the data have been cleaned and prepared for statistical analysis, statistical analyses have been undertaken, and to date two manuscripts have been prepared for publication. (See below for Abstracts of the two manuscripts.) We have also begun analyses of whether use of oral contraceptives brings about weight gain and changes in body composition and whether caffeinated beverages affect bone health.

(b) Abstracts from two manuscripts: We plan to submit two manuscripts in about a month to *Medicine & Science in Sports & Exercise*.

(i) Abstract from manuscript, "Randomized trial of the effect of oral contraceptives on bone mass and stress fractures in female runners:"

Purpose: To determine the effect of oral contraceptives (OCs) on bone mass and stress fracture incidence in young female distance runners. **Methods**: One-hundred fifty competitive female runners aged 18-26 years were randomly assigned to OCs (30 μg ethinyl estradiol and 0.3 mg norgestrel) or control (no intervention) for two years. Bone mineral density (BMD) and content (BMC) were measured by dual x-ray absorptiometry at baseline and at approximately one

year and two years later. Stress fractures were confirmed by x-ray, magnetic resonance imaging, or bone scan. **Results**: Randomization to OCs was unrelated to changes in BMD or BMC in oligo/amenorrheic (n=50) or eumenorrheic runners (n=100). However, treatment-received analyses (which considered actual OC use) showed that oligo/amenorrheic runners who used OCs gained about 1% per year in spine BMD ($p<.005$) and whole body BMC ($p<.005$), an amount similar to those who regained periods spontaneously and significantly greater than those who remained oligo/amenorrheic ($p<.05$). Dietary calcium intake and weight gain independently predicted bone mass gains in oligo/amenorrheic runners, but only calcium intake predicted bone gains in eumenorrheic runners. Randomization to OCs was not significantly related to stress fracture incidence, but the direction of the effect was protective in both menstrual groups (overall hazard ratio [95% CI]: 0.57 [0.18, 1.83]) and the effect became stronger in treatment-received analyses. The statistical power of the trial was reduced by a higher-than-anticipated non-compliance rate. **Conclusion**: OCs may prevent stress fractures in female runners, but our data are inconclusive. Oligo/amenorrheic athletes with low bone mass should be advised to gain weight, increase dietary calcium, and take steps to resume normal menses; they may benefit from OCs, but the evidence is not conclusive.

(ii) Abstract from manuscript, “Risk factors for stress fracture among young female cross-country runners:”

Purpose: To identify risk factors for stress fracture among young female cross-country runners. **Methods:** Participants were 127 competitive female distance runners who were enrolled in a randomized trial of the effects of oral contraceptives on bone health and who were aged 18-26 years at baseline. After filling out a baseline questionnaire and undergoing bone densitometry, they were followed an average of 1.85 years for the occurrence of stress fracture. **Results:** Eighteen participants had at least one stress fracture during follow-up. Baseline characteristics associated ($p<0.10$) in multivariate analysis with stress fracture occurrence were one or more previous stress fractures (rate ratio [RR] [95% confidence interval] = 6.42 (1.80-22.87), lower whole-body bone mineral content (RR = 2.70 [1.26-5.88] per one standard deviation [293.2 grams] decrease), younger chronologic age (RR = 1.42 [1.05-1.92] per one year decrease), lower average daily dietary calcium intake (RR = 1.11 [0.98-1.25] per 100 mg decrease), and younger age at menarche (RR = 1.92 [1.15-3.23] per one year decrease). Although not statistically significant, a history of irregular menstrual periods was also associated with increased rate of stress fracture (RR = 3.41 [0.69-16.91]). Training-related factors did not affect risk. **Conclusion:** The results of this and other studies indicate that risk factors for stress fracture among young female runners include one or more previous stress fractures, lower bone mass, and, although not statistically significant in the present study, menstrual irregularity. More study is needed of the associations between risk for stress fracture according to age, calcium intake, and age at menarche. In light of the

importance of stress fractures to runners, identifying preventive measures is of high priority.

(c) Additional statistical analyses to be undertaken: In addition to completing the analyses we have begun on weight gain and on caffeinated beverages, if we are granted another no-cost extension we would plan to conduct new analyses concerned with several of the following topics: disorder eating, factors other than oral contraceptives that predict changes in body composition (especially in regard to training-related activities), factors that predict spontaneous return of menses, the relation between alcohol consumption and bone health, and the relation between diet and bone health.

(7) KEY RESEARCH ACCOMPLISHMENTS:

A two-year randomized trial of the effect of oral contraceptives on bone mass and stress fracture occurrence in young female distance runners was completed.

Randomization to oral contraceptives was unrelated to changes in bone mineral density or bone mineral content in either oligo/amenorrheic or eumenorrhic runners.

When actual oral contraceptive use was considered (rather than the group to which women were randomly assigned), oligo/amenorrheic runners who used

oral contraceptives gained about 1% spine bone mineral density and whole-body bone mineral content, an amount similar to the gain in those who regained periods spontaneously and significantly greater than those who remained oligo/amenorrheic.

Dietary calcium intake and weight gain were associated with increases in bone mass in oligo/eumenorrheic runners

Dietary calcium intake was associated with increases in bone mass in eumenorrheic runners.

The results suggest that oral contraceptives may protect against stress fractures, but are not definitive.

Risk factors for stress fracture in this study were previous stress fractures, lower bone mass, younger chronologic age, lower dietary calcium intake, and younger age at menarche, and possibly a history of irregular menstrual periods.

Training-related factors were not related to stress fracture risk.

(8) REPORTABLE OUTCOMES Manuscripts to be submitted to *Medicine & Science in Sports & Exercise*:

(1) KRISTIN L. COBB, LAURA K. BACHRACH, MARYFRAN SOWERS, JERI NIEVES, GAIL A. GREENDALE, KYLA K. KENT, W. BYRON BROWN, JR., KATE PETTIT, DIANE M. HARPER, and JENNIFER L. KELSEY. Randomized trial of the effect of oral contraceptives on bone mass and stress fractures in female runners

(2) JENNIFER L. KELSEY, LAURA K. BACHRACH, ELIZABETH PROCTER-GRAY, JERI NIEVES, GAIL A. GREENDALE, MARYFRAN SOWERS, W. BYRON BROWN, JR., KIM A. MATHESON, SYBIL L. CRAWFORD, and KRISTIN L. COBB. Risk factors for stress fracture among young female cross-country runners

(9) CONCLUSIONS (adapted from manuscript Abstracts)

In order to gain bone mass, oligo/amenorrheic athletes with low bone mass should be advised to gain weight, increase dietary calcium, and take steps to resume normal menses; they may benefit from oral contraceptives, but our results are not conclusive. Oral contraceptives may prevent stress fractures in female runners, but our data are again not conclusive. The results of this and other studies indicate that risk factors for stress fracture among young female runners include one or more previous stress fractures, lower bone mass, and, although not statistically significant in the present study, menstrual irregularity. More study is needed of the associations between risk for stress fracture according to age, calcium intake, and age at menarche. Because of difficulty in recruitment and because many young women have reason to switch onto or off oral contraceptives during a trial, it will be difficult to conduct a randomized trial that definitely answers the question of whether use of oral contraceptives protects against loss of bone mass and reduces the risk for stress fractures in young female distance runners.

(10) REFERENCES: None

(11) APPENDICES: See two attached manuscripts.

Randomized trial of the effect of oral contraceptives on bone mass and stress fractures in female runners

KRISTIN L. COBB,[1] LAURA K. BACHRACH,[2] MARYFRAN SOWERS,[3] JERI NIEVES,[4] GAIL A. GREENDALE,[5] KYLA K. KENT,[6] W. BYRON BROWN, JR.,[1,9] KATE PETTIT,[1] DIANE M. HARPER,[7] and JENNIFER L. KELSEY,[1,8]

[1]Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford CA; [2]Department of Pediatrics, Stanford University School of Medicine, Stanford CA; [3]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor MI; [4]Clinical Research Center, Helen Hayes Hospital, West Haverstraw NY and Columbia University, New York NY; [5]Geffen School of Medicine at UCLA, Los Angeles CA; [6]Musculo-Skeletal Research Lab, Stanford University/ Palo Alto Veterans Affairs Medical Health Care Systems, Menlo Park, CA; [7]Norris Cotton Cancer Center, Dartmouth Medical School, Hanover, NH; [8]Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School, Worcester MA; [9]deceased

Corresponding author: Kristin L. Cobb, Division of Epidemiology, HRP Redwood Building, Stanford University, Stanford CA, 94305; Email: kcobb@stanford.edu

Running title: Oral contraceptives and bone health in runners

Purpose: To determine the effect of oral contraceptives (OCs) on bone mass and stress fracture incidence in young female distance runners. **Methods**: One-hundred fifty competitive female runners aged 18-26 years were randomly assigned to OCs (30 μg ethinyl estradiol and 0.3 mg norgestrel) or control (no intervention) for two years. Bone mineral density (BMD) and content (BMC) were measured by dual x-ray absorptiometry at baseline and at approximately one year and two years later. Stress fractures were confirmed by x-ray, magnetic resonance imaging, or bone scan. **Results**: Randomization to OCs was unrelated to changes in BMD or BMC in oligo/amenorrheic (n=50) or eumenorrheic runners (n=100). However, treatment-received analyses (which considered actual OC use) showed that oligo/amenorrheic runners who used OCs gained about 1% per year in spine BMD ($p<.005$) and whole body BMC ($p<.005$), an amount similar to those who regained periods spontaneously and significantly greater than those who remained oligo/amenorrheic ($p<.05$). Dietary calcium intake and weight gain independently predicted bone mass gains in oligo/amenorrheic runners, but only calcium intake predicted bone gains in eumenorrheic runners. Randomization to OCs was not significantly related to stress fracture incidence, but the direction of the effect was protective in both menstrual groups (overall hazard ratio [95% CI]: 0.57 [0.18, 1.83]) and the effect became stronger in treatment-received analyses. The statistical power of the trial was reduced by a higher-than-anticipated non-compliance rate. **Conclusion**: OCs may prevent stress fractures in female runners, but our data are inconclusive. Oligo/amenorrheic athletes with low bone mass should be advised to gain weight, increase dietary calcium, and take steps to resume normal menses; they may benefit from OCs, but the evidence is not conclusive. **Key words:** amenorrhea, oligomenorrhea, bone mineral density, female athlete triad, weight gain, calcium

Introduction

Female athletes with amenorrhea or oligomenorrhea have reduced bone mineral density (BMD) for their age (4,5,9,24,30). Physicians have conventionally treated amenorrheic athletes with hormone therapy or oral contraceptives (OCs) (12), but these treatments are controversial (17). Athletic amenorrhea is strongly related to disordered eating and caloric restriction (5,7, 28), and exogenous estrogens may be ineffective at improving BMD in the absence of improved nutrition and weight gain (7,9,30). Indeed, in non-athletic women with clinically apparent anorexia nervosa, randomized trials have found no effect for hormone therapy or OCs on bone (for a review of these trials, see reference 19). In amenorrheic athletes, one longitudinal study found modest skeletal benefits for hormone therapy (6), but two small randomized trials found no benefit (11,24). Longitudinal studies have also found small to modest skeletal benefits for OCs (4,22,25) and one randomized trial found that OC use reduced bone turnover in amenorrheic athletes, but no randomized trials have evaluated the impact of OCs on BMD in this population.

The effect of OCs on the BMD of eumenorrheic athletes is also unknown. Some eumenorrheic athletes have subclinical menstrual irregularities (e.g., anovulatory cycles) that are associated with an increased risk of bone loss (21), and, hypothetically, OCs might benefit this subgroup. Alternatively, eumenorrheic athletes may be similar to non-athletic premenopausal women, for whom OCs have little effect on bone (19). Lastly, OC use could be detrimental to bone health in exercising women with normal menstrual cycles. Studies from two research groups found that physically active women who used low-dose OCs (<50 μg ethinyl estradiol) had reduced BMD compared with physically active women who did not use OCs (14,15,26) or inactive women (26). To our knowledge, there have been no randomized trials of OC use and BMD in eumenorrheic female athletes.

OC use may also protect against stress fractures in athletes, by affecting bone quality, bone turnover, BMD, or a combination of these (2), but results of previous studies are mixed. One cross-sectional and one case-control study linked OC use to a decrease in stress fracture risk (1,20), but two prospective cohort studies, in athletes (3) and female military recruits (23), found no association. There have been no randomized trials to test this hypothesis.

We conducted a randomized trial to test the effect of OC use on bone mass and stress fracture incidence in female runners. We chose to focus on running to reduce heterogeneity otherwise introduced by multiple sports, and because runners have a high frequency of both amenorrhea and stress fractures.

Materials/methods

Participants and recruitment

The study recruited 150 competitive female runners from inter-collegiate cross country teams, post-collegiate running clubs, and road races mainly in the geographic areas of Palo Alto, CA, Los Angeles, CA, Ann Arbor, MI, West Haverstraw, NY, and Boston, MA. Recruitment took place between August 1998 and September 2003. To be eligible, women had to be 18-26 years old, run at least 40 miles/week during peak training times, and compete in running races. Women were excluded if they had used OCs or other hormonal contraception within six months before entering the study; were unwilling to be randomized to take OCs or not to take them for two years; or had any medical contraindications to OC use. All women were required to visit a study physician or student health service staff member prior to enrollment in the study to rule out contraindications to OC use. Details of the study and testing procedures were explained to each subject, and a written, informed consent was obtained. The protocol was approved by the Institutional Review Boards of Stanford University, the University of California Los Angeles, the University of Michigan, the Helen Hayes Hospital, the Massachusetts General Hospital, the U.S. Army Medical Research and Materiel Command, and the colleges from which participants were recruited.

Randomization and intervention

Eligible women were randomly assigned to receive OCs or no intervention for an intended 2 years, stratified according to clinical site. An independent investigator who was not otherwise affiliated with the study performed the randomization using a random number table. Those assigned to take OCs received the prescription from a study physician or student health service staff member. The OC active ingredients were 30 μg ethinyl estradiol and 0.3 mg norgestrel, (Lo/Ovral, Wyeth Ayerst, 28-day pack). No placebo was used, and neither the athletes nor prescribing physician were blinded to treatment assignment, as it would be unethical to have women unsure of their contraceptive status.

Data collection and follow-up

At baseline, participants visited one of the clinical sites for bone, body composition, and physical measurements. Bone mineral density (BMD), bone mineral content (BMC), and

body composition were measured by dual energy x-ray absorptiometry (see below). Height and weight were measured using standard stadiometers and balance-beam scales, respectively. Participants also filled out questionnaires on menstrual history, previous use of OCs, injury and stress fracture history, training regimen, diet, eating attitudes, and eating behaviors as previously described (5). Women were classified as amenorrheic, oligomenorrheic, or eumenorrheic based on the number of menses they reported having in the previous 12 months (5). Amenorrhea was defined as 0-3 cycles in the past year; oligomenorrhea was defined as 4-9 cycles in the past year; and eumenorrhea was defined as 10 or more cycles in the past year. Participants were asked to return to the same clinical site one year and two years later to repeat these measurements and questionnaires.

There were124 participants (83%) who attended at least one of these follow-up appointments and 96 (64%) participants attended both, at an average of 14.4 months (median: 13.1 months) and 26.6 months (median: 25.4 months), respectively, after baseline. Three additional women provided information on stress fracture occurrence (for an average of 7.9 months after baseline), but did not return for any clinical visits. Baseline characteristics of the 23 participants with no follow-up data were similar to those with follow-up data, except that they were more likely to have a history of stress fracture prior to baseline (52% vs. 32%, p=0.05).

Between clinic visits, participants filled out a monthly calendar on which they recorded menstrual bleeding, use of OC pills, and the occurrence of stress fractures.

Ascertainment of compliance

Women in the treatment group were asked to report if and when they discontinued taking the study medication. Treatment compliance was also monitored through return of used

pill packs, monthly calendars, and yearly questionnaires. If a woman reported having discontinued treatment, she was contacted by a study investigator to determine if and when OCs were discontinued and the reason why. Similarly, women in the control group were asked to contact us if they were planning to start an OC. If so, they were encouraged to take the study pill (Lo/Ovral, Wyeth-Ayerst) or a pill with a similar dose of estrogen. Compliance was also monitored on monthly calendars and yearly questionnaires. If a woman reported having started OCs, she was contacted by a study investigator to get the date of starting OCs, as well as the formulation and the reason for starting them.

Ascertainment of outcomes: Bone mineral density and content

At baseline and each follow-up visit, BMD (g/cm^2) and BMC (g) at the left proximal femur, lumbar spine, and whole body, were measured by dual energy x-ray absorptiometry (DXA, QDR 4500A, Hologic). The coefficient of variation for measuring BMD at the hip and spine in the same person after leaving and then returning to the measuring table on the same day was less than 2% at each of the clinical sites. For most of the periods of data collection, machines were cross-calibrated using a circulating Hologic anthropomorphic spine phantom, and each site maintained a quality assurance program.

Ascertainment of outcomes: stress fractures

Participants were asked to record the occurrence of a possible stress fracture on a monthly calendar and also to report their occurrence to the coordinating center immediately. Participants were also queried periodically about the occurrence of stress fractures by e-mail, phone, and on their questionnaires. Fractures had to be confirmed by x-ray, bone scan, or magnetic resonance imaging to be

counted in this study. All self-reported stress fractures were in fact confirmed. The study paid for the imaging as needed. We included stress fractures that occurred up to one month after the final follow-up visit.

Statistical design and analysis

The trial was designed to have at least 80% power to detect differences in changes in BMD and stress fracture incidence between the OC group and the control group, assuming a 20% annual rate of stress fractures in the control group, a 3-fold difference in stress fracture incidence, and a half-standard deviation difference in changes in BMD, and accounting for anticipated losses to follow-up and noncompliance (we anticipated that 5% of subjects would be lost to follow-up; 20% of treated subjects would discontinue OCs; and 5% of control subjects would begin OCs).

Statistical analyses were performed using the SAS statistical package, version 9.1 (SAS Institute, Cary, NC, U.S.A.). Means were compared between groups using a t-test for normally distributed variables and a Wilcoxon sum-rank test for non-normally distributed variables. Proportions were compared using a chi-square test or a Fisher's exact test, in the case of small cells. For graphing, changes in BMD, BMC, and weight were expressed as annualized percent change since baseline.

All primary outcomes were analyzed according to the intention-to-treat principle. Linear mixed-effects models were used to determine the effect of OCs on changes in BMD and BMC over time. As initially planned, all BMD and BMC analyses were stratified according to baseline menstrual status. The intention-to-treat models included time since baseline in years, treatment group, treatment group × time, and clinical site. A quadratic term for time was tested, but the model fit was found to be inferior. The time term represents the annual rate of change in BMD (or BMC) in the control group; the treatment group × time term represents the difference in annual rates of change in BMD (or BMC) between the treatment and control groups. Cox proportional hazards models were used to determine the effect of OCs on stress fracture incidence. Potential effect modifiers of the relationship between OCs and bone mass or OCs and stress fractures were evaluated by stratifying the model (for categorical variables) or by including an interaction term (for both categorical and continuous variables).

Secondary analyses were performed on the 127 women who provided follow-up data. Per-protocol analyses excluded women from the analysis at the time they switched groups.

Treatment-received analyses grouped women according to their actual use of OCs, or modeled OC use as a time-dependent variable (allowing OC status to change at the dates of starting and stopping OCs). BMD and BMC changes were analyzed by mixed models and stress fracture data were analyzed by Cox proportional hazards models. In mixed models with changes in BMD or BMC as the outcome, calcium intake was adjusted for energy intake by the residual method (27).

Results

Baseline characteristics

One-hundred fifty women were randomized to receive OCs or no intervention (Figure 1). By chance, 69 women were assigned to the OC group and 81 to the control group. The groups were well-balanced on age, race/ethnicity, BMD, stress fracture history, menstrual history, weight and body composition, dietary factors, and training factors (Table 1). Amenorrhea was more common in the OC group and oligomenorrhea was more common in the control group, but the groups were similar in the total proportion of athletes with menstrual irregularity (amenorrhea or oligomenorrhea).

At baseline, amenorrheic women had the lowest BMD on average (spine: 0.932 g/cm^2, hip: 0.937 g/cm^2); oligomenorrheic women had intermediate values (spine: 0.967, hip: 0.972 g/cm^2); and eumenorrheic women had the highest BMD (spine: 0.995 g/cm^2, hip: 0.988 g/cm^2).

Retention and adherence

Twenty-three participants (15%) withdrew or were lost to follow-up after baseline (Figure 1). Reasons for withdrawing included: geographic relocation, pregnancy, illness, and lack of time. Of the remaining 127 participants, 42 (33%) switched groups during the study—25.5% of the treatment group discontinued OCs after an average of 5.4 months of use and 38.9% of the control group started taking them at an average of 11.3 months into the study (Table 2).

Four women in the control group and one woman in the treatment group switched groups twice. The reasons women gave for stopping OCs included (in decreasing order of frequency): fear of weight gain or perceived weight gain, side effects (irritability, abdominal symptoms, nausea, fatigue, or unspecified), and fear of detriment to athletic performance. The reasons control women gave for starting OCs included (in decreasing order of frequency) to: regulate periods, alleviate menstrual symptoms and cramps, prevent pregnancy, treat acne, and treat allergies.

Women who stopped taking OCs showed more signs of the female athlete triad than women who adhered to OCs; they had significantly lower percent body fat, had fewer menstrual periods per year, and had more disordered eating (Table 2). Amenorrheic women were the least likely to comply with taking OCs: of eight amenorrheic women who were assigned to OCs, only one took them through the entire study (of the remaining seven, two were lost to follow-up, five discontinued OCs within two months, and one discontinued OCs after 1.5 years). In the control group, women who self-initiated OC use were less likely than adherent women to have a history of stress fractures prior to baseline.

Primary analysis: Bone mineral content and density

The effect of OCs on bone mass was similar across the clinical sites, so we combined the data from the sites, retaining site as a covariate in all models. Results for spine and hip BMD were similar to results for spine and hip BMC; for comparability with previous studies, we report the BMD results for these sites.

We found that randomization to OCs had no effect on changes in bone mineral content or density—with one exception: in the oligomenorrheic group, total hip BMD was significantly reduced ($p=0.04$) in the OC group compared with the control group (Table 3). This finding may be the result of chance due to multiple comparisons and small numbers. Following correction for multiple comparisons with a Hochberg correction (16), this difference was no longer statistically significant at the .05 level.

Regardless of treatment assignment, bone changes were strongly related to initial menstrual status. Overall, the amenorrheic and oligomenorrheic groups had significant increases

in spine BMD and whole body BMC, with the largest gains occurring in the amenorrheic group. Eumenorrheic women had a small but significant increase in whole body BMC (6.4 ± 2.6 g/year, $p<.05$), but no changes in hip or spine BMD.

We found no interactions between randomization status and age, BMD, weight, weight changes, body composition, disordered eating, calcium intake, or miles run per week with respect to bone outcomes.

Secondary analyses: Bone mineral content and density

One-hundred and twenty-four women had at least one follow-up DXA and were included in secondary analyses. We combined the amenorrheic and oligomenorrheic groups for these analyses because the groups gave similar results when analyzed separately, but the amenorrheic group was too small (n=10) to yield precise estimates in multivariate analyses.

We performed a per-protocol analysis in which women were excluded at the point at which non-adherence was detected. This approach gave similar results to the intention-to-treat analysis (data not shown), except we did not find a negative effect of OCs on hip BMD in oligo/amenorrheic women. Adjusting for clinical site, the treatment effect was: 0.0078 ± 0.0053 g/cm^2/year, p=.15.

Treatment-received analyses also showed no effect for OCs on BMD or BMC in either eumenorrheic (Table 4) or oligo/amenorrheic runners (data not shown). For these analyses, we classified women as being in the OC group if they had used OCs for at least six months during the study. We used a cutoff of six months because it may take this long for OCs to affect bone mineral density. We repeated all analyses using an alternate cutoff of three months or modeling OC use as a time-dependent variable, and found similar results (data not shown).

Fourteen of the oligo/amenorrheic women (4 amenorrheic and 10 oligomenorrheic) regained their periods spontaneously (had 10 or more periods in the year prior to their final measurement), without the help of OCs. When we divided oligo/amenorrheic women into those who had used OCs (for at least six months), those who regained their periods spontaneously, and those whose cycles never normalized, we found that OC users gained more bone than women who remained oligo/amenorrheic (Figure 2). The gain in bone mass among OC users did not differ statistically from women who regained periods spontaneously (Figure 2). On average, both groups gained significant amounts of whole body BMC and spine BMD (but not hip BMD), whereas women who remained oligo/amenorrheic neither gained nor lost bone (Table 4). Average weight gain was (non-significantly) higher in the OC group than the other two groups during the first year of the study (Figure 2), but adjustment for weight changes did not remove the effect of OCs (Table 4). Adjustment for changes in body composition gave similar results (data not shown).

In oligo/amenorrheic women, weight gain independently predicted gains in spine BMD and whole body BMC, and showed a trend at the hip ($p<.10$). Gains in fat mass also independently predicted gains in spine and hip BMD and whole body BMC, but gains in lean mass only predicted gains in whole body BMC (data not shown). Since changes in fat mass and weight were highly correlated ($r=.84$, $p<.0001$), we chose to include weight in the final model because it is a more clinically accessible measure. Higher dietary calcium intake also predicted gains in whole body BMC and hip BMD in oligo/amenorrheic women.

In eumenorrheic women, weight gain was not associated with bone changes, but dietary calcium intake was associated with increases in hip BMD ($p<.05$), and showed a trend for whole body BMC ($p<.10$) (Table 4).

Primary analysis: stress fractures

Eighteen runners had at least one stress fracture during the study in the tibia, foot, or femur. Six occurred in the group randomized to OCs (5.8 per woman-year) and 12 in the group randomized to control (9.2 per woman-year) (Table 5). After adjusting for baseline menstrual status, clinical site, age, prior stress fracture, and spine BMD (the latter two variables were strongly related to fracture risk) in a Cox proportional hazards model, we found that randomization to OCs yielded a non-significant 43% decrease in the rate of stress fracture. This effect was similar across the different clinical sites and across baseline menstrual groups; the hazard ratio (and 95% confidence interval) for eumenorrheic women was: 0.56 (0.14, 2.22), and for oligo/amenorrheic women was: 0.60 (0.06, 5.83).

Women who were oligo/amenorrheic at baseline were not at increased risk of fracture compared with women who were eumenorrheic at baseline (HR: 1.20); however, the majority of oligo/amenorrheic women regained menstrual regularity during the trial. A small group of women who remained oligo/amenorrheic (n=11) or became so during the study (n=2) had a non-significant increase in fracture risk (HR [95% CI]: 2.71 [0.70-10.60]).

We did not find interactions between randomization status and age, low BMD, weight, weight changes, body composition, past menstrual irregularity, disordered eating, calcium intake, or miles run per week with respect to stress fractures, though we had limited statistical power to detect interactions.

Four women had a second stress fracture during the study (three in the control group and one in the treatment group), but this was too few to evaluate statistically.

Secondary analyses: stress fractures

When we excluded non-adherent women from our analysis on the date at which they switched groups, OCs appeared more protective, but did not reach statistical significance (Table 5). We then modeled OC use as a time-dependent variable to ensure that we were only counting OC treatment that occurred prior to each fracture. When women were taking OCs (and had been on them at least a month), OC use appeared to be significantly protective (HR [and 95% CI]: 0.23 [0.06,0.86]). However, four fractures occurred in the control group within the first three months of the study, and it is unclear if these fractures can be attributed to anything other than chance. Excluding these fractures by requiring OC use of at least 3 months reduced the magnitude of the effect slightly and also reduced our statistical power (HR [and 95% CI]: 0.40 [0.11, 1.50]).

Adverse events

There were no serious adverse events in the trial. Five women discontinued OCs citing irritability, abdominal symptoms, nausea, fatigue, or unspecified side effects.

Discussion

We found that randomization to OCs had no effect on BMD or BMC in oligo/amenorrheic or eumenorrheic female runners, and yielded a 43 percent reduction (not statistically significant) in rate of stress fractures across menstrual groups. The trial's statistical power was diminished by non-compliance: 38.9 percent of women in the control group started taking OCs and 25.5 percent of women in the treatment group stopped taking them (among those with follow-up data). Additionally, power was reduced because 38 percent of oligo/amenorrheic runners in the control group resumed normal menses spontaneously. We confirm the difficulties of doing a definitive trial of OCs in female athletes (11).

Contrary to previous reports (14,15,26), we did not find that use of low-dose OCs was detrimental to bone mineral density levels in eumenorrheic female athletes. Some of these previous reports were cross-sectional studies (14,15), which cannot establish the direction of causality and may be confounded by reasons for use of OCs. Because of our choice of study population, we cannot rule out a negative effect of OC use for inactive women who begin an exercise program (26) or for athletes younger than 18 (14).

In our treatment-received analyses, we found that oligo/amenorrheic runners who took OCs for at least six months gained more spine BMD and whole body BMC than runners who remained oligo/amenorrheic, and this association was independent of changes in weight or body composition. The magnitude of the effect—approximately 1% annual gains—was similar to that of regaining periods spontaneously or gaining 5 kg. However, we cannot conclude that OCs per se caused these gains. Women who dropped out of the OC group were more likely to be amenorrheic and have disordered eating, two factors that predispose to continued bone loss or lack of bone growth. Oligo/ameonrrheic runners who adhered to or started on OCs may have been concerned about their bone health and thus actively trying to improve it in other ways not discernible in this study.

Results of previous studies of estrogen supplementation and BMD in amenorrheic athletes have been mixed and may be complicated by the use of different formulations and doses of hormones. Longitudinal cohort studies of OCs (30-35 μg ethinyl estradiol [4,22,25] or hormone therapy (0.625 mg conjugated estrogen or 50 μg estradiol patch [6]) have found small to modest positive effects on BMD in amenorrheic athletes, but these studies may be confounded by other factors associated with the choice to take hormones. Two randomized trials failed to find an effect of hormone therapy (Premarin/Provera and 2 mg estradiol/1 mg estriol, respectively) in 24 amenorrheic ballet dancers (24) and 34 oligo/amenorrheic runners (11). However, similar to our findings with OCs, the latter trial did find a significant benefit for using hormones compared with remaining oligo/amenorrheic in treatment-received analyses.

Our results confirm previous findings that spontaneous recovery of menses benefits the skeleton (8,11,18). In our study, it was unclear why some runners spontaneously resumed normal menses and others did not, and the reasons are likely heterogeneous. Previous researchers have found that decreased training, increased caloric intake, and weight gain predict spontaneous resumption of menses (8,18). We found that, on average, women who spontaneously regained menses had a trend toward higher caloric intake than women who remained oligo/amenorrheic, but this translated to only slightly higher average gains in weight and fat mass. Small improvements in energy balance and eating patterns may normalize menstrual periods without substantial weight gain.

We confirm previous findings that weight gain is an important independent predictor of bone mass gain in oligo/amenorrheic athletes (18); weight gain was associated with increases in whole body BMC, spine BMD, and hip BMD. Fat mass gains were more predictive of changes in BMD and BMC than lean mass gains.

Dietary calcium intake (controlled for energy intake) predicted gains in whole body BMC and hip BMD in both oligo/amenorrheic and eumenorrheic athletes, with a stronger effect in oligo/amenorrheic women. We found no effect for calcium supplementation, but this variable was imprecisely measured, and use of supplements was sporadic in this population. One previous cross-sectional study found a relationship between dietary calcium intake and BMD (29), but these estimates were not adjusted for energy intake. We believe the present study is the first longitudinal study to show that dietary calcium intake is important for continued skeletal mineralization in young adult female runners.

Whole body BMC was significantly increasing over the course of the study in all menstrual groups, thereby indicating continued skeletal mineralization in this age group. Amenorrheic and oligomenorrheic women who recovered their periods (through OCs or spontaneously) gained whole body BMC and spine BMD (but not hip BMD) at a faster rate than eumenorrheic women. This is promising in that it suggests a catch-up effect whereby previously amenorrheic and oligomenorrheic athletes with reduced BMD can gain bone in the third decade of life (9).

This is the first randomized trial to test whether OCs can protect young female athletes against stress fractures. Our results are inconclusive, but show a trend toward protection. In our

intention-to-treat analysis, there was a non-significant 43% reduction in stress fracture incidence among women randomized to OCs. The magnitude of the effect was similar in eumenorrheic and oligo/amnennorheic runners. Follow-up, but not baseline, menstrual irregularity was associated with a non-significant increase in fracture risk.

The effect of OCs on stress fractures became stronger in both per-protocol and treatment-received analyses. In our treatment-received analysis, women were significantly protected against fractures (by 77%) whenever they were taking OCs, though this estimate was weakened when we excluded fractures that occurred early in the trial (58% reduction in risk, p=.20). Our finding may be due to chance or bias. We found that women who switched from the control group to OC use were less likely to have a history of stress fractures prior to joining the study. Thus, the type of woman runner who is willing to continue on or chooses to take OCs may be less prone to fracture for other reasons.

OCs may protect against stress fractures by suppressing bone turnover (25). During bone remodeling, bone resorption precedes bone formation, temporarily leaving skeletal sites weakened and more vulnerable to fracture (2). OCs may also protect against fracture through cumulative effects on BMD (2), but we found no evidence of this in our trial. Finally, OCs may be acting on some other aspect of bone quality that affects fracture risk.

Our findings are consistent with two previous observational studies that found protective effects of similar magnitude. In a case-control study by Myburgh et al. (20), current use of OCs was associated with a 76% reduction in the odds of stress fracture; in a cross-sectional study by Barrow and Saha (1), ever use of OCs (for at least one year) was associated with a 59% reduction in risk of ever having had a fracture. Our findings differ from two prospective cohort

studies who reported no benefit for OCs in track and field athletes and female military recruits (3,23).

Even if OCs confer benefit, women at the highest risk of severe bone deficits and stress fractures may be unwilling to take them. The amenorrheic women in our study had the lowest BMD and were the least willing to take OCs; only one of eight amenorrheic women assigned to OCs took them for the entire study period. Women with disordered eating, considered the precipitating factor in the female athlete triad, were also less likely to continue taking OCs, possibly driven by fear of weight gain.

Our study highlights the difficulty of conducting a randomized trial of OC use in this population. Recruitment for this study took more than five years. Women have strong personal preferences regarding OC use and are reluctant to leave this decision to chance.

Even though this is the largest randomized trial yet of OCs in female athletes (and the largest in oligo/amenorrheic athletes), the trial was likely underpowered for both BMD and stress fracture outcomes, similar to the findings of Gibson et al. (11). Our original sample size calculations greatly underestimated the number of women in the control group who would switch to OCs during the trial, and we did not account for the women in the oligo/amenorrheic group who would spontaneously regain periods and thus obscure our ability to see effects. Despite our best efforts, 15 percent of the study sample provided no follow-up data, which was slightly higher than initially anticipated. The rate of stress fracture in the control group was also lower than anticipated. Based on our results, we estimate that 900 runners would be required to have 80 percent power to detect an effect of OCs on stress fractures in a two-year trial of female runners of any menstrual status. From our study, it is unclear if an adequately powered trial for the effect of OCs on BMD (in oligo/amenorrheic athletes) is even possible; effects may be completely

obscured regardless of sample size because of the high rates of women switching groups or spontaneously regaining menses. Based on their data, Gibson et al. previously estimated that 1150 oligo/amenorheic athletes would be needed (11); given the difficulties that we had recruiting for a trial of 150 runners of any menstrual status, we believe it would be extremely difficult to enroll this many oligo/amenorrheic athletes.

We used an oral contraceptive with 30 μg ethinyl estradiol and 0.3 mg norgestrel. We cannot rule out that different dosages, different routes of administration of hormones, or a different ratio of estrogen to progestin might have more beneficial effects on the skeleton. For example, isolated case reports in amenorrheic women suggest transdermal estrogen may confer more benefits to bone than oral estrogen (13,30).

We did not use a placebo control because of ethical considerations and the high probability of unblinding, as most women would have figured out whether or not they were on OCs by the timing of their menstrual cycles. We did not measure serum hormone concentrations or markers of bone turnover, which may have added information to the study, because these measurements were outside of the study's scope and resources. Finally, our results may not apply to athletes in other sports, since only runners were considered.

In summary, we found that OC use is not detrimental to BMD or BMC in female runners and may protect against stress fractures. Our data suggest that oligo/amenorrheic athletes with low BMD should be advised to gain weight, increase dietary calcium intake, and consider taking OCs if they are unable to establish regular menses on their own. However, we underscore that no clinical trials (including our own) have definitively shown that hormone therapy or OCs increase (or prevent loss of) BMD or BMC in this group. We conclude that it will be difficult to conduct a randomized trial that definitively answers this question.

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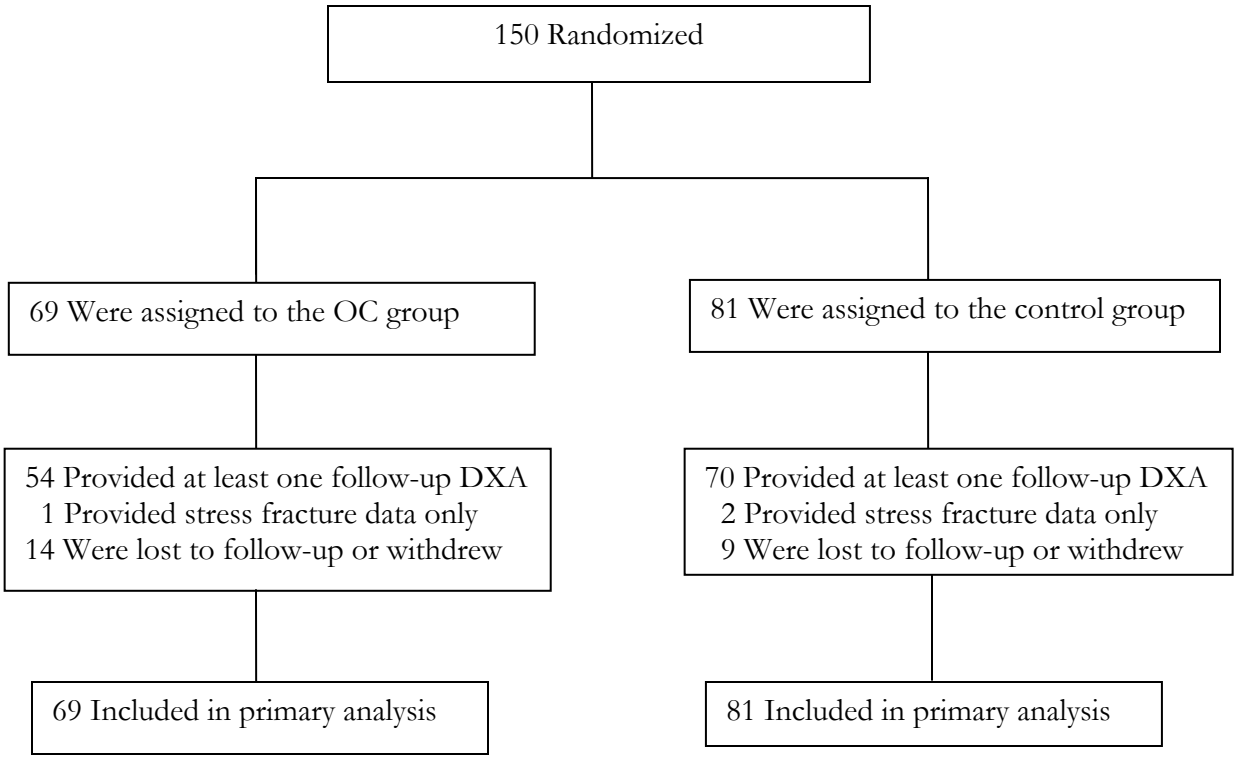


Figure 1**. Flow of participants through the trial.**

TABLE 1. Mean ± one standard deviation or percentage (number) with selected characteristic at baseline, by treatment randomization.

	Treatment randomization	
	Oral contraceptives (n=69)	Control (n=81)
Age (yr)	22.3 ± 2.7	21.9 ± 2.6
Race/ethnicity		
White	82.6% (57)	82.7% (67)
Asian/Pacific Islander	4.4% (3)	9.9% (8)
Hispanic	7.3% (5)	3.7% (3)
Black	2.9% (2)	0% (0)
Other	2.9% (2)	3.7% (3)
Clinical site		
Stanford	53.6% (37)	43.2% (37)
Boston	17.4% (12)	21.0% (17)
Los Angeles	15.9% (11)	21.0% (17)
New York	10.1% (7)	8.6% (7)
Michigan	2.9% (2)	6.2% (5)
Hip BMD (g/cm^2)	0.986 ± 0.119	0.975 ± 0.114
Spine BMD (g/cm^2)	0.979 ± 0.098	0.985 ± 0.112
Whole body bone mineral content (g)	2171 ± 312	2146 ± 279
History of one or more stress fractures	36.2% (25)	33.3% (27)
Age at menarche (yr)	13.1 ± 1.4	13.0 ± 1.5

Total lifetime menstrual periods (no. cycles)	69 ± 28	67 ± 30
Menses in past year (no. cycles)	9.4 ± 3.8	9.5 ± 3.1
Irregular menses		
Amenorrhea *	11.6% (8)	6.2% (5)
Oligomenorrhea †	18.8% (13)	29.6% (24)
Ever used oral contraceptives	43.5% (30)	40.7% (33)
Height (cm)	165.9 ± 6.6	165.4 ± 6.1
Weight (kg)	58.2 ± 7.3	58.1 ± 6.6
Body mass index (kg/m^2)	21.1 ± 1.9	21.3 ± 2.0
Body fat (%)	22.7 ± 5.2	23.3 ± 5.4
Daily caloric intake ($kcal \cdot day^{-1}$)	2250 ± 893	2302 ± 988
Dietary calcium intake ($mg \cdot day^{-1}$)	1394 ± 829	1412 ± 670
Total eating disorder inventory score‡	14.7 ± 14.7	10.6 ± 11.8
Age started running competitively (yr)	14.1 ± 3.8	14.3 ± 3.3
Average distance run per week, past year (miles)	34.8 ± 10.5	34.8 ± 11.4

* 0-3 menstrual periods in the year before baseline.

† 4-9 menstrual periods in the year before baseline.

‡ Total eating disorder inventory score, which can range from 0-69, is the sum of the scores from the anorexia, bulimia, and body dissatisfaction subscales, Garner and Olmstead (10).

TABLE 2. Selected follow-up measures and baseline characteristics according to intervention adherence (where follow-up data were available).

Characteristic	Adherence			
	Adherent to treatment (n=41)	Switched from treatment to control (n=14)	Adherent to control (n=44)	Switched from control to treatment (n=28)
Follow-up measure				
Time in study (months)	24.2 ± 4.7	24.7 ± 8.5	24.0 ± 6.4	25.6 ± 8.3
Time switched groups (months into study)	--	5.4 ± 5.6	--	11.3 ± 10.3
Oral contraceptive use (months)	24.2 ± 4.7	5.4 ± 5.6	0	14.4 ± 9.1
Baseline characteristic				
Age (yr)	22.0 ± 2.7	22.2 ± 2.8	22.1 ± 2.6	21.9 ± 2.8
Hip BMD (g/cm^2)	0.994 ± 0.132	0.962 ± 0.088	0.991 ± 0.115	0.977 ± 0.108
Spine BMD (g/cm^2)	0.984 ± 0.104	0.960 ± 0.103	1.00 ± 0.115	0.985 ± 0.109
Whole body bone mineral content (g)	2157 ± 340	2192 ± 226	2166 ± 243	2181 ± 330

History of one or more stress fractures	34.2% (14)	28.6% (4)	38.6%(17)	17.9% (5)*
Menses in past year (no. cycles)	10.8 ± 2.3	6.3 ± 5.1†	9.6 ± 2.9	9.4 ± 3.4
Irregular menses‡				
Amenorrhea	2.4% (1)	35.7% (5) §	4.6% (2)	7.1%(2)
Oligomenorrhea	14.6% (6)	21.4% (3)	36.4% (16)	25.0% (7)
Weight (kg)	58.6 ± 7.6	57.2 ± 5.4	58.5 ± 6.4	58.4 ± 6.6
Body fat (%)	23.7 ±4.8	19.5 ± 6.1|	23.6 ± 5.5	23.0 ± 5.1
Total eating disorder inventory score**	10.9 ± 11.2	17.4 ± 16.2	12.0 ± 12.4	10.0 ± 11.9
Evidence of prior or current disordered eating^	26.8% (11)	57.1% (8)#	31.8% (14)	32.1% (9)

*p=.06, differs from adherent group, chi-square test

†p<.005, differs from adherent group, Wilcoxon sum-rank test

‡Amenorrhea was defined as 0-3 periods in the year before baseline; oligomenorrhea was defined as 4-9 periods in the year before baseline

§ p<.005, differs from adherent group, Fisher's exact test

| p<.05, differs from adherent group, ttest

**Total eating disorder inventory (EDI) score, which can range from 0-69, is the sum of the scores from the body dissatisfaction, anorexia, and bulimia subscales, Garner and Olmstead (10).

^Women were considered to have evidence of prior or current disordered eating if they scored in the top quartile of the EDI questionnaire (≥ 23) anytime during the study or had a history of anorexia nervosa or bulimia nervosa.

#p<.05, chi-square test

TABLE 3. Annual rate of change* in spine and hip BMD (BMD) and whole body bone mineral content (BMC) by treatment randomization, stratified on initial menstrual status.

	Whole body BMC (g/year ± SE)	Spine BMD (g/cm^2/year ± SE)	Total hip BMD
Amernorrheic[†]			
Treatment (n=8)	16.1 ± 10.3	.0197 ± .0036[**]	.0050 ± .0040
Control (n=5)	28.9 ± 9.9[§]	.0138 ± .0049[§]	.0052 ± .0054
Treatment vs. Control	-12.8 ± 12.4	.0060 ± .0061	-.0002 ± .0067

Oligomenorrheic[‡]			
Treatment (n=13)	23.2 ± 10.4[§]	.0019 ± .0037	-.0096 ± .0033[|]
Control (n=24)	15.3 ± 7.4[§]	.0076 ± .0026[|]	.0012 ± .0023
Treatment vs. Control	8.1 ± 12.8	-.0056 ± .0045	-.01076 ± .0041[§]
Eumenorrheic			
Treatment (n=48)	9.9 ± 3.9[§]	.0022 ± .0019	.0013 ± .0017
Control (n=52)	3.7± 3.4	.0002 ± .0016	-.0023 ± .0015
Treatment vs. Control	6.2 ± 5.2	.0020 ± .0025	.0035 ± .0022

[*] From linear mixed models, adjusted for age and clinical site.

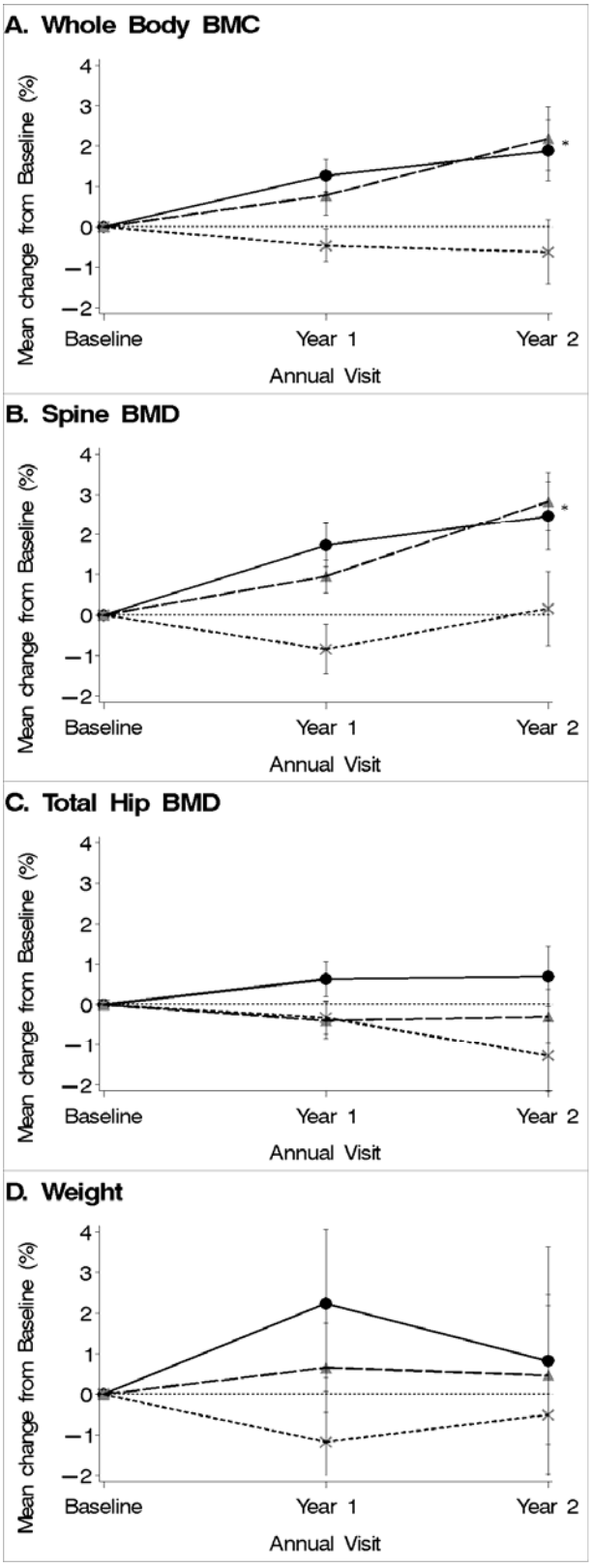
[†] Amenorrhea was defined as 0-3 menses over the past 12 months.

[‡] Oligomenorrhea was defined as 4-9 menses over the past 12 months.

[§] $p<.05$ differs from 0.

[|] $p<.01$ differs from 0.

[**] $p<.0001$ differs from 0.



*p<.05, different than women who remained oligo/amenorrheic, mixed models

Figure 2. Annualized mean percent change in whole body bone mineral content (BMC), spine and hip bone mineral density (BMD), and weight among oligo/amenorrheic women according to follow-up menstrual status (graph displays mean ± one standard error of the mean):

●=Used oral contraceptives at least 6 months (n=16)

▲=Spontaneously regained menses (n=14)

x=Remained oligo/amenorrheic (n=11)

TABLE 4**.** Treatment-received analyses: Adjusted annual rates of change in whole body bone mineral content (BMC) and spine and hip BMD (BMD) among women with at least one follow-up DXA measurement, stratified on initial menstrual status.*

	Whole body BMC (g/year ± SE)	Spine BMD (g/cm^2/year ± SE)	Total hip BMD (g/cm^2/year ± SE)
Oligo/amenorrheic† (n=41)			
Used oral contraceptives for at least 6 months (n=16)	22.4 ± 6.8‡	.0103 ± .0026‡	.0021 ± .0026
Regained periods spontaneously (n=14)	30.4 ± 7.4‡	.0113 ± .0027‡	-.0013 ± .0027
Remained oligo/amenorrheic (n=11)	-4.5 ± 8.9	-.0000 ± .0034	-.0048 ± .0034
Baseline calcium intake (per 1 standard deviation increase) §	10.6 ± 4.9 |	.0020 ± .0018	.0048 ± .0017 |
Weight change (per 5 kg increase)	21.3 ± 8.8 |	.0126 ± .0033‡	.0063 ± .0033**
Eumenorrheic (n=83)			
Used oral contraceptives for at least 6 months (n=50)	10.1 ± 3.5 |	.0024 ± .0017	.0012 ± .0015
Did not use oral contraceptives for at least 6 months (n=33)	4.1 ± 4.4	-.0002 ± .0021	-.0022 ± .0018
Baseline calcium intake (per 1 standard deviation increase) §	4.9 ± 2.7**	.0020 ± 0.0013	.0026 ± .0011 |
Weight change (per 5 kg increase)	-3.6 ± 10.3	.0060 ± .0049	.0060 ± .0043

*Annual rates of change are estimated from linear mixed models, adjusted for clinical site, age, baseline weight, and all other predictors shown in the table.

†Oligo/amenorrhea was defined as 0-9 menses in the year before baseline.

‡ p<.005 rate of change differs from 0.

§Baseline calcium intake is adjusted for caloric intake using the residual method (27). A 1-standard deviation increase was about 550 mg of calcium in this population.

│p<.05 rate of change differs from 0.

** p<.10 rate of change differs from 0.

	Oral contraceptives (n=69)	Control (n=81)	Hazard Ratio (95% CI)*
Analysis			
Intention-to-treat analysis			

TABLE 5. Effect of oral contraceptives on stress fracture incidence according to type of analysis.

Risk Factors for Stress Fracture among Young Female Cross-Country Runners

JENNIFER L. KELSEY,[1,2] LAURA K. BACHRACH,[3] ELIZABETH PROCTER-GRAY,[2] JERI NIEVES,[4] GAIL A. GREENDALE,[5] MARYFRAN SOWERS,[6] W. BYRON BROWN, JR.,[1,7] KIM A. MATHESON,[1] SYBIL L. CRAWFORD,[2] and KRISTIN L. COBB[1]

[1]Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford CA; [2]Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School, Worcester MA; [3]Department of Pediatrics, Stanford University School of Medicine, Stanford CA; [4]Clinical Research Center, Helen Hayes Hospital, West Haverstraw NY and Columbia University, New York NY; [5]Geffen School of Medicine at UCLA; [6,]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor MI; [7]deceased

Corresponding author: Jennifer L. Kelsey, University of Massachusetts Medical School, Department of Medicine, Division of Preventive and Behavioral Medicine, 55 Lake Avenue North, Shaw Building, Worcester MA 01655

Running title: Stress Fractures in Young Female Runner

ABSTRACT

Purpose: To identify risk factors for stress fracture among young female cross country runners. **Methods:** Participants were 127 competitive female distance runners who were enrolled in a randomized trial of the effects of oral contraceptives on bone health and who were aged 18-26 years at baseline. After filling out a baseline questionnaire and undergoing bone densitometry, they were followed an average of 1.85 years for the occurrence of stress fracture. **Results:** Eighteen participants had at least one stress fracture during follow-up. Baseline characteristics associated ($p<0.10$) in multivariate analysis with stress fracture occurrence were one or more previous stress fractures (rate ratio [RR] [95% confidence interval] = 6.42 (1.80-22.87), lower whole-body bone mineral content (RR = 2.70 [1.26-5.88] per one standard deviation [293.2 grams] decrease), younger chronologic age (RR = 1.42 [1.05-1.92] per one year decrease), lower average daily dietary calcium intake (RR = 1.11 [0.98-1.25] per 100 mg decrease), and younger age at menarche (RR = 1.92 [1.15-3.23] per one year decrease). Although not statistically significant, a history of irregular menstrual periods was also associated with increased rate of stress fracture (RR = 3.41 [0.69-16.91]). Training-related factors did not affect risk. **Conclusion:** The results of this and other studies indicate that risk factors for stress fracture among young female runners include one or more previous stress fractures, lower bone mass, and, although not statistically significant in the present study, menstrual irregularity. More study is needed of the associations between risk for stress fracture according to age, calcium intake, and age at menarche. In light of the importance of stress fractures to runners, identifying preventive measures is of high priority. **Key words:** BONE MASS, EPIDEMIOLOGY, FEMALE ATHLETES, LONG DISTANCE RUNNERS

1. Stress fractures are common among young female competitive athletes, especially in track and field (17). Reported one-year incidence rates in competitive track and field athletes have ranged from 8.7% (21) to 21.1% (5) in females and males combined, the variation probably depending in part on the sensitivity of the methods used to detect stress fractures. Incidence rates appear to be similar in female and male track and field athletes (5, 21). It is generally agreed that current or past menstrual irregularity is a risk factor in female athletes (2, 6, 7, 9, 20, 21). Results from studies of female or female and male athletes are contradictory regarding the associations of stress fractures with age (4), lower bone mineral density or lean body mass (6, 7, 9, 21), late age at menarche (4, 6, 7, 9, 20), not using oral contraceptives (4, 7, 20), low body weight (7, 21), disordered eating (6, 7, 21), and low calcium and dairy product intake (6, 7, 20). Individual studies have reported leg length discrepancy (6), low dietary fat intake (6) and a history of stress fracture (21) to be risk factors, but confirmation in other investigations is needed. Many of these results are based on small numbers of study subjects, some have collected information retrospectively, and most do not use multivariate methods of statistical analysis to determine which of these attributes are independent predictors of stress fracture. A recent review in fact concluded that data regarding the epidemiology of stress fractures in athletes are "lacking," except that stress fractures usually occur among those participating in sports with repetitive weight-bearing activity (28). Also, risk factors may not be the same for all athletes, so studies focusing on specific sports may provide particularly useful information for participants in that sport.

2. Studies of stress fracture in female or female and male military recruits and trainees have also produced somewhat inconsistent and tentative results. Possible risk factors include increasing age (18, 26), a small thigh girth (1), lower aerobic fitness (23), no or only a small amount of

lower extremity weight training in the past year (23), lack of menstrual cycles in past year (23), and, in a large prospective study (18), lower bone mineral density, weight loss, alcohol consumption of more than 10 drinks per week, cigarette smoking, weight bearing exercise, lower adult weight, corticosteroid use, use of depo-medroxyprogesterone acetate, and lack of past regular exercise. Two retrospective studies have reported no association between stress fracture occurrence and bone mineral density or bone mineral content (1, 10), and a few studies have found no association with menstrual frequency or age at menarche (1, 18), calcium intake or dairy food consumption (10, 18), and eating disorders (1). In addition to methodologic limitations in some of these studies, risk factors in military recruits and trainees may have limited relevance to women who have been running competitively for several years.

3. In this paper we use data collected during the course of a randomized trial of the effect of oral contraceptives on bone health to identify other factors that predict stress fractures in young female long-distance runners. Results of the randomized trial are presented in a companion paper.

METHODS

4. Study Population: The study population for these analyses consists of 127 competitive female cross-country runners between the ages of 18-26 years at baseline who participated in a randomized trial to examine whether use of oral contraceptives protects against loss of bone mass and stress fracture occurrence. Recruitment took place between August 1998 and September 2003. One hundred fifty runners had been recruited for the trial from intercollegiate cross-country teams, post-collegiate running clubs, and road race participants, of whom 127

(85%) provided some follow-up information. Of these, 57 were collegiate runners and 70 post-collegiate runners. At the time of recruitment, most lived in the vicinities of the sites at which bone densitometry was undertaken: Stanford CA, Los Angles CA, West Haverstraw NY, Ann Arbor MI, and Boston MA. To be eligible, women had to run at least 40 miles per week during peak training times, had to compete in races, could not have used oral contraceptives or other hormonal contraceptives within six months of entering the study, and had to be willing to be randomized and to have no contraindications to oral contraceptive use. The size of the study population was based on the number needed to provide adequate statistical power for the randomized trial, not for the comparisons presented in this paper. The protocol was approved by the Institutional Review Boards of Stanford University, the University of California Los Angeles, the University of Michigan, the Helen Hayes Hospital, the Massachusetts General Hospital, the U.S. Army Medical Research and Materiel Command, and the colleges at which participants were recruited.

5. Data Collected at Baseline: At each of the five clinical sites, height and weight were measured using standard stadiometers and balance-beam scales, respectively. Body mass index (BMI) (kilograms per meter^2) was calculated from these measurements. Body composition (lean body mass and fat mass) and bone mineral content (grams) and bone mineral density (grams/centimeter^2) at the left proximal femur, spine, and whole body and were measured by dual energy x-ray absorptiometry (DXA, QDR 4500A, Hologic). The coefficient of variation for measuring the bone mineral density at the hip and spine in same person after leaving and then returning to the measuring table on the same day was less than 2% at each of the clinical sites. For most of the period of data collection, machines were cross-calibrated using a circulating Hologic anthropomorphic spine phantom, and each site maintained a quality assurance program.

6. A self-administered baseline questionnaire was used to obtain information about several other variables of interest. Demographic information included age and race/ethnicity. Women were asked their age when they first started competing for a running team and number of cross country seasons in which they had competed. They were asked to record the number of miles they ran per week during each competitive season (fall cross-country, winter track, spring track) and off-season (summer) in the previous year. From this information an average number of kilometers run per week was computed for the past year. Participants were asked what percentage of the distance was on pavement or concrete.

7. Women were asked to give a complete history of previous stress fractures that had occurred prior to baseline. They had to report confirmation by x-ray, bone scan, or magnetic resonance imaging for the stress fracture to be counted in these analyses. Eighteen women did not know whether they had experienced a previous stress fracture. These women are assumed not to have had a stress fracture in the analyses presented here.

8. Participants were asked to record their age at menarche and the number of menses they had in the previous 12 months. Women were classified as having current menstrual irregularity if they were oligomenorrheic (defined as 4-9 cycles in the past year) or amenorrheic (defined as fewer than 4 cycles in the past year). Women were also asked whether they had had 0, 1-3, 4-9, or 10-13 menses during each year after menarche. They were categorized as having a history of menstrual irregularity if they had ever been amenorrheic or oligomenorrheic since the year of menarche. A complete history of oral contraceptive use was obtained.

9. A modified version of the 97-item National Cancer Institute Health Habits and History food frequency questionnaire (8) was used to estimate usual nutrient intake during the previous six months. One of the modifications to the questionnaire was the inclusion of additional food items that were likely to be consumed by young athletes and that contained relatively high amounts of calcium. Only dietary calcium intake is included in the analyses presented in this paper. Use of calcium supplements tended to be inconsistent and of short duration, and was not measured precisely enough for inclusion in these analyses. Three subscales (drive for thinness, bulimic tendencies, and body dissatisfaction) of the Eating Disorder Inventory (EDI) were used to identify subclinical eating disorders (3, 14, 15). A total EDI score was computed by summing the scores on each of the three EDI subscales. In the present study Cronbach's alpha for the three subscales was 0.79, indicating that the scores for the three subscales were to a large extent consistent with the total score.

10. Ascertainment of Stress Fracture Occurrence During Follow-up: Participants were asked to record the occurrence of a possible stress fracture on a monthly calendar and also to report their occurrence to us immediately. The fracture had to be confirmed by x-ray, bone scan, or magnetic resonance imaging to be counted in this study. All reported stress fractures were in fact confirmed. The study paid for the imaging as needed. Participants were also queried periodically about the occurrence of stress fractures by e-mail, phone, and on their questionnaires. No additional stress fractures were reported as a result of these queries.

11. Other Aspects of Follow-up: Participants were asked to return for bone densitometry and measurement of body composition, height, and weight one year and two years after baseline measurements. At this time they were asked to fill out a questionnaire covering most of the areas

included at baseline, and every six months they filled out another food frequency questionnaire. This information is not, however, used in the present analyses. Because the data were updated only at yearly intervals (or in the case of dietary intake at six month intervals), it was generally not possible to know whether any changes preceded or followed stress fracture occurrence, and therefore it was impossible to differentiate cause from effect.

12. In addition, in this young, mobile, and preoccupied population, not all participants had measurements made at the time requested. As mentioned above, no follow-up information at all was available for 23 (15%) of the original 150 women seen at baseline, and some were followed for less than two years. Baseline characteristics of those lost to follow-up were generally similar to those retained in the cohort, except that those lost to follow-up were more likely to have a history of stress fracture prior to baseline (52% vs. 32%, p=0.05). Among those who continued to participate in the study, we set a four-year limit as to how long we would wait for them to report for their follow-up visits. Only four runners had their final follow-up visit during the fourth year. Also, we included stress fractures that occurred up to one month after the final follow-up visit.

13. Statistical Analysis: Analyses were carried out with the SAS statistical package, version 8.02 (SAS Institute, Cary NC). Cox proportional hazards models were used to compute rate ratios for the rate of a first stress fracture during follow-up among those with a given characteristic divided by the rate of a first stress fracture during follow-up among those without the characteristic. Cox models were also used to estimate rate ratios according to the level of a characteristic and to compute rate ratios for one variable while controlling for the effects of other characteristics. Except for descriptive information on the study population, all analyses

controlled for clinical assessment site and group to which a participant was randomized. No significant statistical interactions by treatment assignment or clinical site were found, but power to detect such interactions was low. Additional control on actual oral contraceptive use during follow-up did not materially change any of the results. An examination of the degree of skewness of the variables indicated that none needed to be transformed.

RESULTS

14. The 127 participants were followed for stress fracture occurrence for a total of 2824 months, or an average of 1.85 years per woman. The age at baseline of the 127 runners ranged from 18 to 26 years, with a mean of 22.0 years. Table 1 provides other descriptive statistics on the cohort at baseline. About 83% were white, and their average body mass index was 21.2 kg/m^2. Almost 31% reported having previously had one or more definite stress fractures, 57% had a history of menstrual irregularity, and 40% had previously used oral contraceptives.

15. Eighteen of the 127 runners had at least one stress fracture, for an average of 7.7 first stress fractures during the follow-up period per 100 person-years of follow-up. Ten of the first stress fractures occurred in the tibia, six in the foot, and two in the femur. Four runners had a second stress fracture: two in the tibia, one in the foot, and one in the femur.

16. Table 2 shows rate ratios for first stress fracture during the observation period according to characteristics ascertained at baseline. Women with a previous stress fracture had more than a six-fold higher rate of stress fracture during follow-up than women without such a history. Various indicators of lower bone mass were associated with an increased rate of stress fracture.

For instance, for each standard deviation decrease (293.2 grams) in whole body bone mineral, the rate of stress fracture increased by almost twofold. Other factors associated ($p < 0.10$) with an increased rate of stress fracture were lower average daily dietary calcium intake and daily servings of dairy products, younger age at menarche, lower lean body mass, and lower weight. Younger age, shorter height, lack of previous oral contraceptive use, and a history of menstrual irregularity were also associated with increased rates of stress fracture, but these trends were not statistically significant. Little association was seen for current menstrual irregularity, percent body fat, BMI, age started running competitively, total competitive seasons run, kilometers run per week in past year, and total eating disorder inventory score from the three subscales.

17. We used a multivariate Cox model to identify variables that predicted stress fracture independently of the other variables under consideration. The various indicators of bone mass at different skeletal sites were highly correlated with each other, and we selected whole-body bone mineral content for our primary multivariate model because of the strength of its association with stress fracture, the multiple skeletal sites at which stress fractures can occur, and the limitations of using bone mineral density as a measure of bone mass, particularly when growth is still occurring (16). We subsequently present another model in which hip bone mineral density is used in place of whole-body bone mineral content because some readers will have a preference for that measure. Daily calcium intake and servings of dairy products were highly correlated ($r = 0.83$), and we chose dietary calcium intake for the multivariate model. Lean body mass was sufficiently highly correlated with bone mineral content that it could not be included in the same model. Accordingly, age, height, weight, history of stress fracture, age at menarche, history of menstrual irregularity, whole-body bone mineral content, and daily calcium in the diet were considered for inclusion in a multivariate model, along with certain other variables. Those

significant at $p < 0.10$, and also a history of menstrual irregularity, for which the rate ratio was consistent with other studies even though $p > 0.10$, were included in the model presented here.

18. Table 3 shows that among these variables, a history of stress fracture was still a strong predictor of a future stress fracture, along with lower whole-body bone mineral content, decreasing age, younger age at menarche, and lower dietary calcium intake. A history of irregular periods was also associated with an increase rate of stress fracture, although not statistically significantly so. Height, weight, BMI, percent body fat, age started running competitively, total competitive seasons run, kilometers run per week in past year, and total eating disorder inventory score did not predict stress fracture occurrence when entered into the multivariate analysis.

19. Table 4 shows the multivariate model obtained when hip bone mineral density was substituted for whole-body bone mineral content. Similar results were obtained.

DISCUSSION

20. To our knowledge only one other study in runners, presented in abstract form (21), has examined whether a history of stress fracture predicts future stress fracture, and a positive association was found. A study in military recruits (23) reported an increase in risk that did not reach statistical significance. The rate ratio of 6.42 (1.80-22.87) associated with one or more previous stress fractures in the multivariate analysis here indicates that particular attention should be paid to this history, as these individuals appear to be at especially high risk of additional stress fractures. Our results also indicate that a history of stress fractures is a marker of susceptibility

above and beyond its association with bone mineral content or density and the other variables included in the multivariate analyses. Runners and their coaches should be made aware of the high risk for additional fractures, should try to identify the reason for the high risk, and make changes so as to reduce that risk.

21. Our finding that lower bone mass is associated with an increased risk for stress fracture is consistent with other prospective studies carried out in competitive athletes (6, 21) and military recruits (18). Thus, it is likely that lower bone mass is indeed predictive.

22. Several previous studies in competitive athletes and military recruits have reported that current or past menstrual irregularity is associated with an increased risk for stress fracture (2, 6, 7, 9, 20, 21, 23). Our rate ratio of 3.41 (0.69-16.91), although not statistically significant, is consistent with these other reports. Studies not finding this association had very small numbers of amenorrheic participants (18) or had participants with only short periods of amenorrhea (10). Menstrual irregularities often occur in association with low serum estrogen concentrations and are known to be related to low bone mineral density and low serum concentrations of bone formation markers (12, 19, 22, 29). The results of our multivariate analysis suggest that a history of menstrual irregularity may have additional adverse effects on bone geometry beyond its associations with lower bone mineral content and density. Efforts should be made to identify reasons for the menstrual irregularities, such as inadequate diet, and appropriate changes made.

23. Low calcium and dairy product intake has been associated with decreased bone mineral density in young adult women (24). Some studies in competitive athletes have found lower calcium and dairy product intake to be associated with an increased risk for stress fracture (7,

20), while another study in track and field athletes (6) and studies in military recruits (10, 18) have not. The prospective study of Bennell et al. (6) reported that most of the track and field athletes had high intakes of dietary calcium, and were thereby probably already receiving whatever protection dietary calcium provides against stress fracture. The questionnaire used in another study (18) assessed only whether the recruits had at least one serving of milk, cheese, or yogurt per day, and thus did not attempt to collect detailed quantitative information on calcium intake. The other study (10) asked soldiers to recall diet during adolescence, and errors in recall would have been likely. Nevertheless, uncertainty remains about the role of lower calcium intake on stress fracture occurrence. In our study lower dietary calcium and dairy product intake were associated with an increased risk of stress fracture independently of their association with bone mineral content or density. Some other aspect of bone strength may be affected by calcium intake as well. For instance, insufficient dietary calcium would also be expected to result in inadequate repair of microdamage (20) or may have a detrimental effect on some aspect of bone geometry, such as cortical thickness (25), and thereby increase the risk for stress fractures. Increasing calcium intake in those consuming inadequate amounts would be a relatively easy preventive measure to implement, so determining its importance with more certainty is of high priority.

24. Whether increasing age is associated with a greater risk, a reduced risk, or no change in risk for stress fracture has been controversial (4). Across the age range of 18-26 years considered in this study, it would be expected that younger runners would have higher stress fracture rates because bone mass is still gained through the third decade of life (24). It should also be noted that the decreasing stress fracture rate with increasing age in the present study was seen only in the multivariate analysis when we accounted for a history of stress fracture.

25. Other studies of athletes in this age group (4, 6, 7, 9, 20) have found either a positive association between age at menarche and stress fracture risk or no association. In contrast, we found that younger age at menarche was associated with a higher rate of stress fracture. Most studies, but by no means all (reviewed in 4, 13), have found that age at menarche is inversely correlated with bone mineral density and bone mineral content, but in the present study we found that age at menarche had only a slight inverse correlation with whole-body bone mineral density ($r=-0.13$, $p=0.12$), but no correlation with whole-body bone mineral content ($r=0.03$, $p=0.76$). If later age at menarche results in later maturation and consolidation of bone, one would expect higher rates of stress fracture with later age at menarche, as reported by others. It is possible that some other aspect of bone strength associated with late age at menarche is playing a role in the decreased risk found in our study. Among the determinants of bone strength are bone size, cortical thickness and porosity, the number of trabeculae, trabecular thickness and connectedness, tissue mineral content, the presence of microfractures, and the direction and extent of cross-linking of collagen (27). Further studies are needed before any definitive conclusions are reached.

26. Although we previously reported an association at baseline between disordered eating and low bone mineral density among eumenorrheic runners (11), no association between disordered eating and subsequent stress fracture occurrence was seen in these analyses. Numbers of stress fractures, however, were too small to consider the rates of stress fracture by menstrual status and eating disorder status simultaneously.

27. Finally, we did not find training-related factors to be important, including age started running competitively, total competitive seasons run, miles run per week in past year, and miles run on concrete or pavement. The number of stress fractures was too small to enable us to examine these factors in detail, but the results of the present study are consistent with those reported by others (6, 20). Although it does not appear that training-related factors are important in the etiology of stress fracture at least among athletes who have been participating in their sport for several years, more study with larger numbers of stress fractures and with more variation in length and type of training is needed before definitive conclusions are reached.

28. Our prospective study had the advantage of collecting information on possible risk factors before the occurrence of the stress fractures, thus eliminating the possibility of biased recall once a stress fracture has occurred. In addition, all participants were from one sport, cross-country running, thus eliminating sport as a potential source of variation. On the other hand, our study population was of modest size, consisted of runners willing to participate in a randomized trial, and the number of stress fractures was only 18. Accordingly, we could not identify small increases or decreases in risk. Also, despite our best efforts, we had no follow-up information on 15% of the original participants. We found this age group, with its high degree of mobility and changing interests over time, to be particularly challenging to retain in a longitudinal study. Finally, because the major objective was to conduct a randomized trial of the effect of oral contraceptives, we did not collect information on a wide spectrum of possible risk factors.

29. In conclusion, the results of our study and those of others indicate that young female runners with previous stress fractures, lower bone mass, and a history of irregular menstrual periods are at high risk for stress fracture and should be carefully monitored. Although the evidence is not

definitive, adequate dietary calcium intake should be encouraged. The relation between age at menarche and risk for stress fracture is unclear, and needs further study.

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TABLE 1. Mean ± one standard deviation or percentage with selected characteristic at baseline

Characteristic	**Mean ± 1 Standard Deviation or Percentage**
Age (years)	22.0 ± 2.6
Height (cm)	165,9 ± 6.1
Weight (kg)	58.3 ± 6.7
Body mass index (kg/m^2)	21.2 ± 1.9
Percent body fat	23.0 ± 5.3%
Race/ethnicity	
White	83.5%
Hispanic	3.9%
Asian/Pacific Islander	8.7%
Black	0.8%
Other	3.1%
Age started running competitively (years)	14.2 ± 3.5
Total number seasons run competitively	11.9 ± 6.8
Average distance run per week, past year (km)	55.5 ± 18.0
Percent of distance on pavement or concrete	65.6 ± 22.1%

History of one or more stress fractures	30.7%
Age at menarche (years)	13.1 ± 1.5
History of menstrual irregularity*	57.1%
Menstrual irregularity (past year)†	33.1%
Ever used oral contraceptives	39.7%
Total eating disorder inventory score‡	11.8 ± 12.4
Whole-body bone mineral content (g)	2169.3 ± 293.2
Bone mineral density (g/cm^2)	
Hip	0.986 ± 0.116
Spine	0.988 ± 0.108
Whole body	1.111 ± 0.084
Daily dietary calcium intake (mg)	1357.5 ± 681.4

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* ≤ 9 menstrual periods in any year, excluding the year of menarche.

† ≤ 9 menstrual periods in the year before baseline.

‡ Total eating disorder inventory score, which can range from 0-50, is the sum of the scores from three subscales. See Garner and Olmstead (14).

TABLE 2. Adjusted* rate ratios (and 95% confidence interval) for associations between selected characteristics and stress fracture

Characteristic	Rate Ratio (95% CI)
Age (per year younger)	1.12 (0.89,1.41)
Height (per cm shorter)	1.04 (0.96, 1.12)
Weight (per kg decrease)	1.08 (0.99, 1.16)
Body mass index (per kg/m^2 decrease)	1.20 (0.90, 1.61)
Percent body fat (per 5 % increase)	1.16 (0.71, 1.89)
Lean body mass (per kg decrease)	1.14 (1.01, 1.28)
Age started running competitively (per year younger)	1.01 (0.93, 1.10)
Total number competitive seasons (per season)	1.01 (0.93, 1.10)
Average distance run per week, past year (per 10 km increase)	1.08 (0.81, 1.45)
Percent distance on pavement or concrete (per 5% decrease)	1.05 (0.94, 1.18)
History of one or more stress fractures (yes/no)	6.38 (1.97, 20.6)
Number of previous stress fractures (per each previous fracture)	1.59 (1.15, 2.19)
Age at menarche (per year younger)	1.37 (0.97, 1.92)
History of menstrual irregularity† (yes/no)	1.90 (0.66, 5.51)
Menstrual irregularity in past year‡ (yes/no)	1.05 (0.38, 2.89)
Never used oral contraceptives (yes/no)	2.22 (0.65, 7.69)
Total eating disorder inventory score§ (per 5 units)	1.03 (0.86, 1.24)

Whole-body bone mineral content (per standard deviation decrease, where 1 standard deviation = 293.2 g)	1.79 (1.02, 3.13)
Hip bone mineral content (per standard deviation decrease, where 1 standard deviation = 5.78 g)	1.69 (0.95, 2.94)
Spine bone mineral density (per standard deviation decrease, where 1 standard deviation = 0.11 g/cm^2)	1.89 (1.04, 3.45)
Hip bone mineral density (per standard deviation decrease, where 1 standard deviation = 0.12 g/cm^2)	1.45 (0.81, 2.56)
Whole body skeletal area (per standard deviation decrease, where 1 standard deviation = 166.8 cm^2)	1,89 (1.06. 3.33)
Daily dietary calcium intake (per 100 mg decrease)	1.08 (0.99, 1.18)
Daily servings of dairy products (per one serving decrease)	1.41 (1.01, 1.96)

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*Adjusted by Cox proportional hazards model for clinical site and treatment group assignment.

† ≤ 9 menstrual periods in any year, excluding the year of menarche.

‡ ≤ 9 menstrual periods in the year before baseline.

§ Total eating disorder inventory score, which can range from 0-69, is the sum of the scores from three subscales. See Garner and Olmstead (14).

TABLE 3. Multivariate adjusted* rate ratios (and 95% confidence intervals) for associations between selected characteristics and stress fracture, whole body bone mineral content used as measure of bone mass

Characteristic	Rate Ratio (95% CI)
Age (per year younger)	1.42 (1.05, 1.92)
History of one or more stress fractures (yes/no)	6.42 (1.80, 22.87)
Whole-body bone mineral content (per standard deviation decrease, where 1 standard deviation = 293.2 g)	2.70 (1.26, 5.88)
Daily dietary calcium intake (per 100 mg decrease)	1.11 (0.98, 1.25)
Age at menarche (per year younger)	1.92 (1.15, 3.23)
History of menstrual irregularity† (yes/no)	3.41 (0.69, 16.91)

*Adjusted by Cox proportional hazards model for clinical site, treatment group assignment, and all the other variables in the table.

† ≤ 9 menstrual periods in any year, excluding the year of menarche.

TABLE 4. Multivariate adjusted* rate ratios (and 95% confidence intervals) for associations between selected characteristics and stress fracture, hip bone mineral density used as measure of bone mass

Characteristic	Rate Ratio (95% CI)
Age (per year younger)	1.42 (1.03, 1.95)
History of one or more stress fractures (yes/no)	6.71 (1.93, 23.35)
Hip bone mineral density (per standard deviation decrease, where 1 standard deviation = 0.12 g/cm^2)	2.16 (1.04, 4.48)
Daily dietary calcium intake (per 100 mg decrease)	1.09 (0.97, 1.23)
Age at menarche (per year decrease)	1.61 (1.04, 2.49)
History of menstrual irregularity† (yes/no)	3.10 (0.70, 13.74)

*Adjusted by Cox proportional hazards model for clinical site, treatment group assignment, and all the other variables in the table.

† ≤ 9 menstrual periods in any year, excluding the year of menarche.